REMARKS

Claims 1-20 were pending in this application. Claims 6, 13 and 18-20 are withdrawn. Claims 2, 3, 5, 8 and 12-16 are now cancelled without prejudice to Applicants' right to prosecute their subject matter in the present application and in related applications. New claims 21-27 are added. Claims 1, 4, 6, 9-11 and 17 are amended without any intent of disclaiming equivalents thereof. Accordingly, upon entry of this paper, claims 1, 4, 7, 9-11, 17 and 21-27 are pending and presented for consideration.

Claim Amendments

Support for amendments to claim 1 can be found throughout the specification at least, for example, in paragraphs 0005, 0006, 0017, 0020, 0030, 0039 and Table 5.

Support for amendments to claims 10 and 11 can be found in the specification at least, for example, in paragraph 0039.

Support for amendments to claim 17 can be found throughout the specification at least, for example, in paragraphs 0020, 0021, 0030, 0039 and Example 3.

Claims 4, 6 and 9-11 are also amended for clarification and consistency.

Support for new claim 21 can be found in the specification at least, for example, in paragraph 0050 and Table 5.

Support for new claims 22-27 can be found in the specification at least, for example, in paragraphs 0029 and 0039.

Applicants submit that the amendments to the claims introduce no new matter.

Information disclosure statement

Applicants submit together with this response a supplemental Information Disclosure Statement and accompanying Form PTO-1449 listing publications in accordance with the provisions of 37 C.F.R. §§ 1.97 and 1.98 for consideration by the Examiner in connection with the examination of the present patent application.

Oath/Declaration

The Office Action requires a new oath/declaration in compliance with 37 C.F.R. §1.67(a) identifying this application by application number and filing date. The Office Action also indicates that the oath/declaration currently on file is defective because it does not identify the citizenship of each inventor.

Applicants thank Examiner Schlapkohl for speaking with the undersigned attorney on June 28, 2007, regarding the new oath/declaration required by the Office Action. The undersigned attorney indicated to Examiner Schlapkohl that Applicants are in the process of contacting the inventors in the present application to execute a supplemental declaration in compliance with 37 C.F.R. §1.67(a) as required by the Office Action and requested the objection be held in abeyance. Examiner Schlapkohl kindly agreed that he will hold this objection in abeyance at this time. Applicants will submit a supplemental declaration when all the inventors have signed the supplemental declaration.

Claim objections

Claim 4 is objected to because the acronym RCC recited in the claim should be spelled out at its first occurrence. Applicants have amended claim 4 to spell out the acronym RCC.

Claim 9 is objected to because the acronym RT-PCR should be spelled out at its first occurrence. Applicants have amended claim 9 to spell out the acronym RT-PCR.

Accordingly, Applicants respectfully request the claim objections be withdrawn.

Claim rejections under 35 U.S.C. §112, second paragraph

Claims 1-3, 8-10, 12 and 14-16 stand rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 3, 8, 12 and 14-16 have been cancelled without prejudice and without acquiescing to the rejections; therefore, all rejections with respect to these claims are moot.

The Office Action alleges that claim 1 is vague and indefinite in that the metes and bounds of the term "non-blood disease" are unclear. The Office Action also alleges that it is not

clear how the phrase "wherein the patient has the non-blood disease and is being treated by said drug therapy" modifies the claim. Applicants have amended claim 1 to delete the term "non-blood disease" and the phrase "wherein the patient has the non-blood disease and is being treated by said drug therapy."

The Office Action alleges that claim 9 is unclear because "the expression profile" lacks clear and positive antecedent basis. Applicants have amended claim 9 to specifically recite "the expression profile of the at least one CCI-779 activity gene generated in step (a)" to provide clear and unambiguous antecedent basis.

The Office Action also alleges that claim 10 is vague and indefinite for reciting "wherein the reference expression profile is an average expression profile of said at least one gene in peripheral blood samples isolated from said patients before said drug therapy" because, according to the Office Action, the metes and bounds of an "average expression profile" are unclear. Applicants have amended claim 10 to delete the term "average expression profile." Amended claim 10 now recites "wherein the reference expression profile is a baseline expression profile of said at least one CCI-779 activity gene in a peripheral blood samples isolated from said patient before CCI-779 treatment."

Accordingly, Applicants respectfully request the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 1-5, 7-12 and 14-17 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Office Action alleges that the claimed method proposes to use any "drug activity gene" as a biomarker or surrogate endpoint for efficacy in the treatment of any non-blood disease with any drug therapy. *See*, the Office Action, page 14. The Office Action then relied on Wagner, (2002) Dis. Markers, 18(2):41-46, Frank *et al.* (2003) Nature Rev., 2:566-580, Feng *et al.* (2004) Pharmacogenomics, 5:709-719, and Twine *et al.* (2003) Cancer Research, 63(18):6069-6075 to show that it is highly unpredictable as to the use of biomarkers to determine disease state and efficacy of drug therapy. See, the Office Action, pages 14-17.

Without acquiescing to the rejection and solely to advance prosecution, Applicants have cancelled claims 2, 3, 5, 8 and 12-16 without prejudice. Thus, the rejections with respect to claims 2, 3, 5, 8 and 12-16 are moot. Applicants traverse the rejection to the extent it is maintained over the remaining claims as amended.

The test for enablement is whether one reasonably skilled in the art could make or use the invention as broadly as it is claimed based on the disclosures in the specification coupled with information known in the art without undue experimentation. See *In re* Wands, 858 F.2d 731 (CAFC 1988).

Claims 1, 4, 7 and 9-11

Independent claim 1, as amended, recites the following:

> 1. A method for detecting *in vivo* CCI-779 activity in a patient having a solid tumor, the method comprising:
>
> (a) generating an expression profile of at least one CCI-779 activity gene selected from Table 5 in a peripheral blood sample obtained from the patient having the solid tumor and at a stage of treatment with CCI-779;
>
> (b) comparing the expression profile of said at least one CCI-779 activity gene generated in step (a) to a reference expression profile of said at least one CCI-779 activity gene; and
>
> (c) detecting *in vivo* CCI-779 activity in the patient based on the comparison result from step (b), wherein a statistically significant change in the expression profile of said at least one CCI-779 activity gene compared to the reference expression profile is indicative of the *in vivo* CCI-779 activity.

Thus, amended claim 1 recites a method for detecting *in vivo* CCI-779 activity in a patient having a solid tumor by generating an expression profile of at least one CCI-779 activity gene selected from Table 5 in a peripheral blood sample obtained from the patient having the solid tumor and at a stage of treatment with CCI-779 and comparing the expression profile to a reference expression profile, wherein a statistically significant change in the expression profile of said at least one CCI-779 activity gene compared to the reference expression profile is indicative of the *in vivo* CCI-779 activity. In other words, amended claim 1 recites a method for simply detecting the presence of *in vivo* CCI-779 activity based on the expression profile of specific

CCI-779 activity genes selected from Table 5, *i.e.*, genes specifically modulated by *in vivo* CCI-779 activity. Contrary to the Office Action's allegation, amended claim 1 does not require using any "drug activity gene" as a biomarker or surrogate endpoint for efficacy in the treatment of any non-blood disease with any drug therapy. Amended claim 1 also does not require determining disease state or efficacy of drug therapy, as discussed in Wagner, Frank, Feng or Twine relied on by the Office Action. Therefore, Applicants submit that the unpredictability as to the use of biomarkers to determine disease state and efficacy of drug therapy does not apply to amended claim 1.

Applicants submit that the present specification fully enables one of skill in the art to practice the method as claimed in claim 1 for the following reasons. First, the CCI-779 activity genes recited in claim 1 are genes that are specifically modulated by *in vivo* CCI-779 activity identified by the present invention. The names and sequences of such CCI-779 activity genes are provided in Table 5. Therefore, one of ordinary skill in the art, upon reviewing the specification, would readily have understood which CCI-779 activity gene to look at. Secondly, the present specification provides sufficient guidelines on how to generate an expression profile of at least one CCI-779 activity gene selected from Table 5 in a peripheral blood sample obtained from the patient having the solid tumor and at a stage of treatment with CCI-779. For example, methods for generating expression profiles are described at least in paragraphs 0022-0027, 0422-0453 and Examples 1 and 2. Methods for obtaining peripheral blood samples from the patient at different stages of treatment of CCI-779 are described at least in paragraphs 0028 and 0029. Thirdly, the present specification provides sufficient guidelines on how to compare the expression profile of the at least one CCI-779 activity gene to a reference expression profile and to detect a statistically significant change in the expression profile based on the comparison result. For example, methods for comparing the expression profile of a sample of interest to a reference expression profile are described in paragraphs 0454-0460 and Example 3. Methods for detecting statistically significant difference between the expression profile and the reference expression profile are provided in paragraphs 0458 and 0467-0467. Therefore, Applicants submit that one of ordinary skill, upon reviewing the specification, would readily have been able to carry out the method as claimed in claim 1 without undue experimentation.

For at least the above reasons, Applicants respectfully submit that the present application fully complies with the enablement requirement with respect to independent claim 1 and its dependent claims 4, 7, 9-11 and 21-23 and request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claim 17

Independent claim 17, as amended, recites the following:

> 17. A method for identifying genes modulated by CCI-779, the method comprising:
>
> (a) obtaining a peripheral blood sample from a patient having a solid tumor and at a stage of treatment with CCI-779;
>
> (b) generating an expression profile of the peripheral blood sample obtained in step (a); and
>
> (c) comparing said expression profile generated in step (b) to a reference expression profile of a reference peripheral blood sample from said patient to identify one or more differentially expressed genes.

Thus, amended claim 17 recites a method for identifying genes modulated by CCI-779 by generating an expression profile of a peripheral blood sample obtained from a patient having a solid tumor and at a stage of treatment with CCI-779 and comparing the expression profile to a reference expression profile to identify one or more differentially expressed genes. Contrary to the Office Action's allegation, amended claim 17 does not require using any "drug activity gene" as a biomarker or surrogate endpoint for efficacy in the treatment of any non-blood disease with any drug therapy. Amended claim 17 also does not require determining disease state or efficacy of drug therapy, as discussed in Wagner, Frank, Feng or Twine relied on by the Office Action. Therefore, Applicants submit that the unpredictability as to the use of biomarkers to determine disease state and efficacy of drug therapy does not apply to amended claim 17.

Applicants further submit that the present specification fully enables one of skill in the art to practice the method as claimed in claim 17 for the following reasons. First, the present specification provides sufficient guidelines on how to generate an expression profile in a peripheral blood sample obtained from a patient having a solid tumor and at a stage of treatment with CCI-779 and to compare it to a reference expression profile to identify one or more

differentially expressed genes. For example, methods for generating expression profiles are described at least in paragraphs 0022-0027, 0422-0453 and Examples 1 and 2. Different stages of CCI-779 treatment are described in paragraphs 0029 and 0039. Methods for comparing the expression profile of a sample of interest to a reference expression profile are described in paragraphs 0454-0460 and Example 3. Guidelines on how to detect differentially expressed genes are provided in paragraphs 0458 and 0467-0467. Furthermore, the present specification provides numerous working examples of genes modulated by CCI-779 identified by the method as claimed in claim 17. For example, exemplary genes modulated by CCI-779 are shown in Tables 2-6. Therefore, Applicants submit that one of ordinary skill, upon reviewing the specification, would readily have been able to carry out the method as claimed in claim 17 without undue experimentation.

For at least the above reasons, Applicants respectfully submit that the present application fully complies with the enablement requirement with respect to independent claim 17 and its dependent claims and request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claim rejection under 35 U.S.C. §102

Claims 1, 9-11 and 17 stand rejected under 35 U.S.C. §102(b) as being anticipated by DiPaola *et al.* (J. Clin. Oncol. 17(7):2213-2218). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

For a rejection to be proper under 35 U.S.C. §102, each and every element of the claimed invention must be identically disclosed or described in a single prior art reference. *In re Bond,* 910 F.2d 831, 832, 15 U.S.P.Q.2d (BNA) 1566, 1567 (Fed. Cir. 1990) (quoting *Diversitech Corp. v. Century Steps, Inc.,* 850 F.2d 675, 677, 7 U.S.P.Q.2d (BNA) 1315, 1317 (Fed. Cir. 1988). Emphasis added.

As discussed above, independent claim 1, as amended, recites a method for detecting *in vivo* CCI-779 activity in a patient having a solid tumor by generating an expression profile of at least one CCI-779 activity gene selected from Table 5 in a peripheral blood sample obtained from the patient having the solid tumor and at a stage of treatment with CCI-779 and comparing

the expression profile of said at least one CCI-779 activity gene to a reference expression profile, wherein a statistically significant change of the expression profile of said at least one CCI-779 activity gene compared to the reference expression profile is indicative of the *in vivo* CCI-779 activity. DiPaola teaches pharmacodynamic studies to show that 13-*cis*-retinoic acid (CRA) and interferon alfa (IFNα) can modulate BCL-2 expression *in vitro* and in tumor patients. *See, e.g.*, DiPaola, abstract, and page 2213-2214. DiPaola however does not teach or suggest a method for detecting *in vivo* CCI-779 activity by generating an expression profile of at least one CCI-779 activity gene selected from Table 5 as required by claim 1. In fact, DiPaola does not teach or suggest any method for detecting *in vivo* CCI-779 activity whatsoever. Therefore, Applicants submit that DiPaola fails to anticipate claim 1 and its dependent claims because DiPaola does not teach or suggest at least one required element. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Similarly, independent claim 17, as amended, recites a method for identifying genes modulated by CCI-779 by obtaining a peripheral blood sample from a patient having a solid tumor and at a stage of treatment with CCI-779, generating an expression profile of the peripheral blood sample obtained from the patient and comparing it to a reference expression profile to identify one or more differentially expressed genes. As discussed above, DiPaola teaches pharmacodynamic studies to show that 13-*cis*-retinoic acid (CRA) and interferon alfa (IFNα) can modulate BCL-2 expression *in vitro* and in tumor patients. *See, e.g.*, DiPaola, abstract, and page 2213-2214. DiPaola does not teach or suggest a method for identifying genes modulated by CCI-779 by obtaining a peripheral blood sample from a patient having a solid tumor and at a stage of treatment with CCI-779, generating an expression profile of the peripheral blood sample obtained from the patient and comparing it to a reference expression profile as required by claim 1. In fact, DiPaola does not teach or suggest any method for identifying genes modulated by CCI-779 whatsoever. Therefore, Applicants submit that DiPaola fails to anticipate claim 17 and its dependent claims because DiPaola does not teach or suggest at least one required element. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

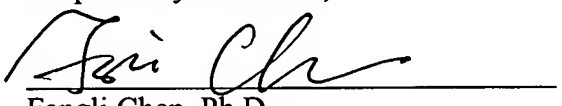
Double Patenting

Claims 1-4 and 10-11 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-3 of co-pending application, U.S. Serial No. 10/793,032. Applicants request that the provisional nonstatutory obviousness-type double patenting rejection be held in abeyance until such time that the presence of otherwise-allowable subject matter is acknowledged. At such time, Applicants will file an appropriate terminal disclaimer over the co-pending application, U.S. Serial No. 10/793,032.

CONCLUSION

In view of the foregoing, Applicants believe that all rejections have been overcome and claims 1, 4, 7, 9-11, 17 and 21-27 are in condition for allowance. The Examiner is invited to telephone the undersigned attorney to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,



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